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Curcumin Analogs in Glioblastoma Therapy: A Narrative Review

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Abstract

Glioblastoma (GBM) is an aggressive and treatment-resistant primary brain tumor with a poor prognosis. Conventional therapies are limited by tumor heterogeneity, therapy resistance, and restricted Blood-Brain Barrier (BBB) penetration, highlighting the need for novel multi-targeted therapeutic strategies. This review assesses the therapeutic potential of curcumin analogs in GBM, with a focus on their molecular mechanisms, in silico predictions, preclinical efficacy, and potential synergistic strategies with standard treatments. A comprehensive search of published in vitro, in vivo, and computational studies on curcumin analogs was conducted. Mechanistic investigations included apoptosis induction, cell-cycle arrest, autophagy, ferroptosis, and inhibition of key oncogenic pathways such as STAT3, NF-κB, PI3K/Akt/mTOR, and EGFR. Pharmacokinetic optimization and BBB permeability were also assessed. Curcumin analogs demonstrate enhanced cytotoxicity in GBM cells, including temozolomide-resistant lines, through multi-target modulation of apoptosis, oxidative stress, oncogenic signaling, and glioma stem cell pathways. in silico docking and network pharmacology reveal strong binding to GBM-relevant targets, corroborating experimental efficacy. Preclinical studies show that analogs such as C-150, ALZ003, and DMC-BH suppress tumor growth, inhibit angiogenesis, and prolong survival in orthotopic and xenograft models. Combination with temozolomide, radiotherapy, or anti-angiogenic agents exhibits synergistic anti-tumor effects. Curcumin analogs are promising multi-targeted agents capable of overcoming GBM heterogeneity, therapy resistance, and invasiveness. Optimization of pharmacokinetics and targeted delivery, along with clinical evaluation, is necessary to translate preclinical findings into effective GBM therapies. Glioblastoma (GBM) is a highly aggressive type of brain cancer characterized by treatment resistance and a poor prognosis. The efficacy of conventional treatment approaches is limited by treatment resistance, heterogeneity, and inability to cross the Blood-Brain Barrier (BBB). Therefore, there is a need to develop new multi-targeting treatment approaches. This review aims to describe the therapeutic potential of curcumin analogs for GBM treatment, focusing on their molecular mechanisms, in silico studies, and their potential to act synergistically with conventional treatment approaches. A comprehensive literature review of published studies on curcumin analogs was conducted. Mechanistic studies of curcumin analogs included induction of apoptosis, cell cycle inhibition, induction of autophagy, and ferroptosis, as well as inhibition of key oncogenic pathways, including STAT3, NF-κB, PI3K/Akt/mTOR, and EGFR. In addition, studies aimed at improving their pharmacokinetics and permeability through the BBB were included. Evidence from various studies

indicates that curcumin analogs exhibit superior cytotoxic effects against GBM cells, including temozolomide-resistant GBM cells, through multi-targeting approaches. In addition, in silico studies have demonstrated high binding affinities to key GBM-related targets. Preclinical studies have demonstrated the efficacy of curcumin analogs, including C-150, ALZ003, and DMC-BH, in inhibiting GBM growth, angiogenesis, and improving survival in orthotopic and xenograft mouse models. These compounds have demonstrated synergistic effects with temozolomide, radiotherapy, and anti-angiogenic therapy. Therefore, curcumin analogs have demonstrated significant therapeutic potential as multi-targeting agents to address heterogeneity, treatment resistance, and invasiveness of GBM. However, to realize this potential, there is a need to improve their pharmacokinetics and permeability through the BBB.

Keywords: EF24; Glioblastoma multiforme; bisdemethoxycurcumin; curcumin analog; demethoxycurcumin; difluorinated curcumin.; tetrahydrocurcumin.